made in the outstanding Official Action. Accordingly, applicants have proceeded herein on this basis.

The Patent Office has issued a final Official Action. Claims 1-11, 13-23 and 39-66 are newly rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 1-11, 13-23 and 25-38 remain rejected under 35 U.S.C. § 102(b) as being anticipated by the journal article LeCluyse et al. (1994) *Am. J. Physiol.* 266:C1764-C1774 (herein after LeCluyse et al. [U]) and/or by the abstract Liu et al. (1997) *Pharm. Res.* 24:S-459 (hereinafter Liu et al. [EE]). Claims 39-64 remain rejected under 35 U.S.C. 102(a) as being anticipated by the abstract Liu et al. (1998) *Pharm. Sci.* 1:S-119 (hereinafter Liu et al. [CC]. Claims 1-11, 13-23, and 25-66 are rejected under 35 U.S.C. § 103(a) as being unpatentable over LeCluyse et al. [U] and/or Liu et al. [IDS-EE] in view of U.S. Patent No. 5,602,026 to Dunn et al. (hereinafter Dunn et al. [A]), Liu et al. (1996) *Pharm. Res. Init.* 13:S-393 (8003) (hereinafter Liu et al. [IDS-DD], and Poole et al. (1990) *Archives of Toxicology* 64:474-481 (hereinafter Poole et al. [U]).

The amendments to the claims presented herein are intended to more particularly point out and distinctly claim the subject invention. No new matter has been added by virtue of any of the amendments to the claims. Reconsideration of the present U.S. patent application as amended and based on the arguments set forth below is respectfully requested.

Telephone Interview Summary

A telephone interview was scheduled and conducted on Friday, May 17, 2002. Participating in the telephone interview were Examiners Vera Afremova and Jon Weber of the United States Patent and Trademark Office, applicants Dr. Kim L.R. Brouwer and Dr. Edward L. LeCluyse, and applicants' counsel Arles A. Taylor, Jr. Claims 1, 13, 25, and 39 were discussed. Cited documents Liu, et al. [EE], LeCluyse et al. [U], and Liu, et al. [CC] were discussed. Applicants wish to extend their most sincere thanks to Examiners Afremova and Weber for their time and consideration in conducting the Telephone Interview.

Pages Showing Changes Made

Pursuant to 37 CFR § 1.121, attached hereto is a marked-up version of the claims, which illustrates all of the changes made thereto. The attached page is captioned "Version With Markings To Show Changes Made". Deleted language is bracketed and added language is underlined.

Response to the Rejection of Claims Under

35 U.S.C. § 112, Second Paragraph

The Patent Office has rejected pending claims 1-11, 13-23 and 39-66 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that applicants regard as the invention. More specifically, the Patent Office asserts that independent claims 1, 13, 39 and 52 are rendered indefinite by the phrase "normalized" upon the contention that this phrase encompasses an uncertain range of normalized amounts and methods for determining normalized amounts.

Applicants respectfully do not agree that the recitation of the term "normalized" is indefinite. However, in an effort to expedite allowance of the subject U.S. patent application, claims 1-11, 13-23 and 39-66 have been canceled herein without prejudice to the filing of a continuing application directed thereto. Accordingly, this rejection is believed to be rendered moot.

Response to the Rejection of Claims Under 35 U.S.C. Section 102(b)

Based on LeCluyse et al. [U] or Liu et al. [EE]

Claims 1-11, 13-23, and 25-38 remain rejected under 35 U.S.C. Section 102(b) as being anticipated by LeCluyse et al. [U] and/or Liu et al. [EE]. The Patent Office asserts that LeCluyse et al. [U] and/or Liu et al. [EE] disclose identical active steps and identical structural elements of the subject invention as claimed. More specifically, the Patent Office asserts that LeCluyse et al. [U] discloses a method of screening candidate compounds for susceptibility to biliary excretion, and that Liu et al. [EE] discloses a method of screening a plurality of candidate compounds for susceptibility to biliary excretion. This rejection is

respectfully traversed.

Applicants respectfully do not agree that LeCluyse et al. [U] and Liu et al. [EE] teach a method of screening compounds *in vitro* for determining the susceptibility of a compound to *in vivo* biliary excretion, in accordance with the present invention. However, in an effort to expedite allowance of the subject U.S. patent application, claims 1-11, 13-23 and 39-66 have been canceled herein without prejudice to the filing of a continuing application directed thereto. Accordingly, this rejection is believed to be rendered partially moot.

Claims 25-38

Claim 25 recites a competition assay in accordance with the present invention, wherein a candidate compound and a marker compound compete for uptake and excretion to thereby provide a method of screening a candidate compound for susceptibility to biliary excretion that is amenable to high throughput techniques. Step (d) of claim 25 recites that the detection of the marker compound is performed to evaluate uptake and excretion competition between the candidate compound and the marker compound. Support for this recitation can be found in the subject U.S. Patent Application as filed at page 22, line 8 through page 24, line 22, and particularly at page 22, line 20 through page 23, line 2.

In contrast, LeCluyse et al. [U] describes a method for monitoring the uptake and excretion of a single compound in a hepatocyte culture. The Patent Office contends that this distinction is not convincing because "the method of the cited reference encompasses the same steps as [the] presently claimed method including exposure of hepatocytes culture to both marker and candidate compounds at least during some period of culturing hepatocytes." Official Action, page 4, paragraph 1. Applicants respectfully submit that this contention is conclusory and unsupported by the LeCluyse et al. [U] reference. Specifically, LeCluyse et al. [U] does not teach, suggest, or motivate a step of providing a candidate compound and a marker compound to a hepatocyte culture, as recited in step 25(b), but describes only provision of a single compound (a fluorescent dye), whether that single compound be called a marker compound or a candidate

compound, to a hepatocyte culture. Further, the Patent Office has not supported its contention by reference to specific text within the cited reference.

To still more particularly point out the competitive nature of the assay method recited in claim 25, step (b) of claim 25 has been amended to recite "simultaneously exposing a candidate compound and a pre-selected amount of a marker compound that is a substrate for an endogenous sinusoidal or canalicular transport system, or for both sinusoidal and canalicular transport systems to the culture for a time sufficient to allow uptake." Support for this amendment can be found in the application as originally filed, for example at page 22, lines 9-19 of the application as originally filed. The preamble of claim 25 and step (d) of claim 25 have been similarly amended. Thus, amended claim 25 is believed to be further distinguished over the method of LeCluyse et al.[U], where there is no indication that the multiple compounds employed in the method include a candidate compound and a marker compound, wherein an amount of the marker compound is indicative of an amount of biliary excretion of the candidate compound.

In addition, LeCluyse et al.[U] does not describe the step (d) of claim 25 of the present invention, which recites detecting an amount of marker compound. As described further herein above and incorporated herein by reference, the LeCluyse et al. [U] reference teaches detection of the presence or absence of marker compound, but does not teach determination of an amount of compound. Thus, claim 25 is believed to be patentably distinguished over the LeCluyse et al. [U] reference in accordance with 35 U.S.C. § 102(b). Claims 26-38 are dependent upon claim 25, and thus are also believed to be patentably distinguished over the LeCluyse et al. [U] reference.

Liu et al. [EE] discloses a method for monitoring the uptake and excretion of several candidate compounds in a hepatocyte culture, but does not disclose determining an amount of a marker compound, wherein the amount of the marker compound is indicative of the susceptibility of a candidate compound to biliary excretion *in vivo*. The Patent Office contends that this distinction is not convincing because "the method of [the cited reference] encompasses evaluation of uptake and excretion of several compounds including markers and/or radiolabeled

compounds." Official Action, page 4, paragraph 1. Applicants respectfully submit that the brevity of the cited reference is such that the it remains unclear whether the model compounds were provided to the culture together or separately, and how such variable provision might be useful for determining biliary excretion. In the absence of such instruction, Liu et al. [EE] does not provide a competitive assay format as recited in claim 25.

Based on the foregoing arguments, applicants respectfully submit that Liu et al. [EE] expressly does not disclose step (d) of claim 25 of the present invention: detecting an amount of marker compound present in the at least one bile canaliculus in the culture, the presence or the absence of a reduced amount of the marker compound as compared to the pre-selected amount of marker compound indicating the susceptibility of the candidate compound to biliary excretion. Thus, claim 25 is believed to be patentably distinguished over the Liu et al. [EE] reference in accordance with the requirements of 35 U.S.C. § 102(b). Claims 26-38 are dependent upon claim 25, and thus are likewise believed to be patently distinguished over the Liu et al. [EE] reference.

In summary, LeCluyse et al. [U] and Liu et al. [EE] do not teach a competition assay as recited in claim 25, wherein a candidate compound and a marker compound compete for uptake to thereby provide a method of screening a candidate compound for susceptibility to biliary excretion. Therefore, claim 25 is believed to be patentably distinguished over LeCluyse et al. [U] and Liu et al. [EE]. Claims 26-38 are dependent upon claim 25, and thus, claims 26-38 are likewise believed to be patentably distinguished over LeCluyse et al. [U] and Liu et al. [EE]. Applicant respectfully requests that the rejection of claims 25-38 under 35 U.S.C. Section 102(b) be withdrawn. Allowance of claims 25-38 is also respectfully requested.

Response to the Rejection of Claims Under 35 U.S.C. § 102(a)

Based on Liu et al.[CC]

Claims 39-64 remain rejected under 35 U.S.C. § 102(a) as being anticipated by Liu et al. [CC]. The Patent Office alleges that Liu et al. [CC] discloses identical

active steps and identical structural elements of the subject invention as claimed. The Patent Office also contends that the disclosure of the previously submitted Affidavit does not appear to contain subject matter encompassed by claims 39-64 such as an *in vitro* evaluation of "biliary clearance" of a candidate compound in a hepatocyte culture. Official Action, page 5, paragraph 4.

Applicants respectfully do not agree that Liu et al. [CC] teaches a method of screening compounds *in vitro* for determining the susceptibility of a compound to *in vivo* biliary excretion, in accordance with the present invention. However, in an effort to expedite allowance of the subject U.S. patent application, claims 39-66 have been canceled herein without prejudice to the filing of a continuing application directed thereto. Accordingly, this rejection is believed to be rendered moot.

Response to the Rejection of Claims Under 35 U.S.C. Section 103(a) Based on LeCluyse et al.[U] and/or Liu et al.[EE] in view of Liu et al.[EE], Poole et al.[V], and Dunn et al. [A]

Claims 1-11, 13-23, and 25-66 are rejected under 35 U.S.C. Section 103(a) as being unpatentable over LeCluyse et al. [U] and/or Liu et al. [EE] in view of Liu et al. [DD], Poole et al. [V], and Dunn et al. [A].

Applicants respectfully do not agree that the cited combination of LeCluyse et al. [U] and/or Liu et al. [EE] in view of Liu et al. [DD], Poole et al. [V], and Dunn et al. [A] teach a method of screening compounds *in vitro* for determining the susceptibility of a compound to *in vivo* biliary excretion, in accordance with the present invention. However, in an effort to expedite allowance of the subject U.S. patent application, claims 1-11, 13-23 and 39-66 have been canceled herein without prejudice to the filing of a continuing application directed thereto. Accordingly, this rejection is believed to be rendered partially moot.

Claims 25-38

Claim 25 recites a competition assay in accordance with the present invention, wherein a candidate compound and a marker compound are competed

against each other to provide a method of screening a candidate compound for susceptibility to biliary excretion that is amenable to a high throughput screening approach. According to the method, both a candidate compound and a marker compound are added to the culture for a time sufficient to allow for uptake so that the candidate compound and marker compound compete for uptake in the culture of hepatocytes. To particularly point out the competitive nature of the assay method recited in claim 25, step (b) of claim 25 has been amended to recite "simultaneously exposing a candidate compound and a pre-selected amount of a marker compound that is a substrate for an endogenous sinusoidal or canalicular transport system, or for both sinusoidal and canalicular transport systems to the culture for a time sufficient to allow uptake." The preamble of claim 25 and step (d) of claim 25 have been similarly amended. Support for this amendment can be found in the application as originally filed, for example at page 22, lines 9-19 of the application as originally filed.

By the arguments set forth herein above and incorporated herein by reference, LeCluyse et al. [U] and Liu et al. [EE] do not teach a competition assay as disclosed by the present invention, wherein a candidate compound and a marker compound are simultaneously exposed to a hepatocyte culture and compete for uptake to thereby provide a method of screening a candidate compound for susceptibility to biliary excretion. Similarly, Liu et al. [DD], Poole et al. [V], and Dunn et al. [A] do not suggest these deficiencies and also fail to disclose a competition assay as recited by claim 25.

The simultaneous provision of a candidate compound and a marker compound to a hepatocyte culture and the evaluating of uptake and excretion competition between the candidate compound and the marker compound is not disclosed in LeCluyse et al. [U], Liu et al. [EE], Liu et al. [DD], Poole et al. [V], or Dunn et al. [A], when taken individually or in combination. Thus, a combination of any or all of the references cited by the Patent Office does not render claim 25 obvious in that such a combination fails to teach all of the elements of the present invention. Thus, applicants respectfully request that the rejection of claim 25 under 35 U.S.C. §103(a) be withdrawn. Applicants also respectfully request that

claim 25 be allowed.

Claims 26-38 are ultimately dependent on patentably distinguished claim 1. Claims 26-38 are thus also believed to be patentably distinguished over the cited combination in view of this dependency. Withdrawal of the rejection of claims 26-38 under 35 U.S.C. §103(a) and allowance of claims 26-38 are also respectfully requested.

CONCLUSION

In light of the above Amendments and Remarks, it is respectfully submitted that the present application is now in a proper condition for allowance and such action is earnestly solicited. If any minor issues should remain outstanding after the Patent Examiner has had an opportunity to study the above Amendments and Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney so that all such matters may be resolved and the application be placed in a condition for allowance without the necessity for issuance of another Official Action.

The Commissioner is hereby authorized to charge any deficiencies of payment or credit any overpayments associated with the filing of this Amendment to Deposit Account No. 50-0426.

Respectfully submitted,

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